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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LAMBERTSON, DAVID A	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 11/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/977,693	STAMLER, JONATHAN S.	
	Examiner	Art Unit	
	David A. Lambertson	1636	

-- The MAILING DATE of this communication appears on th cover sh t with the corr spond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) *11 and 12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group II (claims 1-10) is acknowledged. The traversal is on the ground(s) that it would not be an undue burden for the USPTO to examine all of the claims. The rationale behind the traversal is that the different groups are (1) classified into the same class and subclass, (2) contain overlapping claims, and (3) both compare physiological and pathophysiological processes. This is not found persuasive because of the following reasons:

1. First, the different groups are not classified into the same class and subclass. Each of the groups has a distinct subclass, reflecting the differences in the claimed subject matter. It is unclear why applicant is of the opinion that 435/6 and 435/7.1 are the same class and subclass. Furthermore, even in instances where the class and subclass are identical (which they are not), if the non-patent literature searches were significantly different (as would be the case in the instant scenario), this would require an undue search burden, thereby justifying a restriction.

2. Second, the claims overlap because there are multiple inventions contained within those claims. This is clearly set forth in the restriction requirement and by the different sub-classifications of the claims as it regards the distinct subject matter contained in the overlapping claims. Specifically, methods of using nucleic acids (i.e., genomic) and methods of using proteins (i.e., proteomic) require different searches, as established by the different sub-classifications.

3. Third, the restriction requirement clearly sets forth that different modes of operation are required in the methods that compare physiological and pathophysiological conditions, thereby justifying a restriction requirement.

Finally, it is noted that the claims have been amended to retract the non-elected subject matter of claims 1-4, which are the only overlapping claims. Therefore, the traversal is moot based on the amendment.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-12 are pending in the instant application. Claims 11 and 12 are withdrawn as being drawn to a non-elected invention. Claims 1-10 are ready for examination with respect to establishing a proteomic interaction map.

Information Disclosure Statement

The information disclosure statement filed as January 10, 2002 as Paper No. 2 has been considered, and a signed and initialed copy of the form PTO-1449 has been attached to this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation (*United States v. Telectronics.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based upon a single factor but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), and the most relevant factors are indicated below:

Nature of the invention. The nature of the invention is a method of establishing a protein interaction map comprising interactions that occur under physiological/non-disease conditions and interactions that occur under any pathophysiological/disease conditions that are related to redox state perturbations. The invention is also directed to the identification of proteins that are involved in any disease state, where the disease state is mimicked by a change in redox state. In specific embodiments (i.e., claims 5-10), the applied conditions relate to oxygen tension levels. The protein interaction map can then be used to compare the protein interactions that occur (or, in theory, do not occur) under the disease conditions relative to the non-disease conditions with the intention of identifying disease markers (see for example the Abstract). The protein interaction map is preferably determined using a two-hybrid system, more specifically a yeast two-hybrid system (see for example page 9, lines 11-20 of the instant specification). The

specification asserts that "current screening methodology lacks a level of validation and biological significance" because "[T]he actions and interactions are not causally related to the pathophysiological processes" (see for example the second paragraph of the instant specification); this is because the interaction screens are carried out in air, and do not administer an environment that is characteristic of the disease. The current invention, because it recognizes and applies environments of a perturbed redox state, overcomes these flaws in the current screening processes by establishing a causal relationship between protein interactions and disease states.

Scope of the invention. The scope of the invention is very broad, encompassing subject matter that is not disclosed in the specification. Specifically, the claims indicate that virtually any disease state can be compared to a non-disease state simply by altering the redox environment in which an interaction occurs. However, it is unclear what pathophysiological processes can be examined simply by changing the redox environment. This is because there are a multitude of pathological conditions that arise from genetic alterations, and have nothing to do with redox environment (e.g., genetic mutations in p53 give rise to particular forms of cancer, and this unrelated to redox state; for review, see Wynford-Thomas *et al. Carcinogenesis* **19**:29-36, 1998). Without a clear indication of what diseases can be examined under altered redox conditions, the skilled artisan would be unable to use the claimed invention because the skilled artisan would not know for which disease they were establishing a protein interaction map. Similarly, it is unclear what particular redox conditions would be relevant to a given disease. In other words, at what level of perturbation does a redox condition represent a disease state (and what particular diseases does it relate to).

Number of working examples and Guidance provided by applicant. The instant specification briefly describes some examples of a method of establishing a protein interaction map that can prospectively be used for the comparison of physiological and pathological processes. In all instances, the methods involve the use of a yeast two-hybrid system. In the most explicitly described method, the interactions between proteins "known to be involved in apoptosis" and a macrophage mRNA library (i.e., the proteins encoded by these mRNAs) were tested via a yeast two-hybrid system under physiological conditions and under pathophysiological conditions. A particular interaction that is identified occurs between caspase (a protein known to be involved in apoptosis) and an unknown protein that is also proposed to be involved in apoptosis based solely on sequence homology (see for example page 22, lines 8-11). However, there is no clear indication in the specification that this protein was actually involved in apoptosis, nor was there an indication that the interaction between this protein and caspase affected apoptosis in anyway. Furthermore, the lack of an identification of this unknown protein prohibits the examination of the prior art as to the unknown protein's ability to function during apoptosis. In fact, there is no indication that any of the 18 interactions that were identified by the method are biologically relevant, let alone indicative of a causal relationship as it regards a diseased state. These obstacles provide a great deal of unpredictability as it relates to the claimed method, which requires that a causal relationship be established between protein interactions and diseased states. In other words, in order for the claimed method to have an enabled use, the skilled artisan must be able to compare the interactions between proteins that occur in the diseased versus non-diseased states, and establish that the interactions identified in the comparison are specific and biologically relevant to the diseased states. The examples and

guidance presented in the instant specification do not clearly establish a biological relevance to the interactions, as is supported in the evaluation of the State of the Art and the Unpredictability of the Invention (see below). Thus, the skilled artisan would need to consult the prior art in an attempt to overcome these obstacles in order to make and use the claimed invention.

State of the art and Level of skill in the art. The instant specification makes use of a two-hybrid assay in a method to establish a protein interaction map to compare physiological and pathophysiological conditions with the hopes of establishing a causal relationship between particular protein-protein interactions and a disease state. The State of the art indicates that the use of the two-hybrid system to generate a protein interaction map has many pitfalls (see for example Ito *et al. PNAS* **97**: 1143-1147, 2000; see entire document; henceforth Ito).

Ito teaches a method toward a protein-protein interaction map, where the interactions are established by a yeast two-hybrid system (see for example the Abstract). However, Ito recognizes several problems that exist in their method (see broadly, the Discussion). Specifically, Ito states that the interactions that they identify are only *candidate interactions* that *may be* of biological significance (see for example page 1147, left column first complete paragraph). This is because the yeast two-hybrid system suffers not only from false positives that may represent meaningless interactions (see for example page 1147, left column, second full paragraph), but also suffers from false negatives, or interactions that escape detection (see for example page 1147, the paragraph bridging the left and right columns). These false negatives include problems surrounding the detection of interactions with membrane proteins (such as ligand-receptor interactions) because the detection system in a yeast two-hybrid system requires nuclear localization, and membrane proteins could only localize to the nucleus upon unfolding

and removal from the cell membrane, thereby resulting in non-biologically relevant interactions (see for example page 1147, the paragraph bridging the left and right columns). Finally, Ito raises the question of interactions that do not occur directly, but are instead mediated by third-party endogenous proteins (see for example page 1147, right column, first full paragraph). This is of particular importance to the instant invention because the interactions that are being tested occur between mammalian proteins (e.g., proteins from a macrophage); since only the two mammalian proteins being tested for an interaction are present in the yeast cell, there are a number of interactions that may go undetected because of the lack of third-party contributors.

Applicant's primary working example describes what might appear to be the successful identification of a biologically relevant interaction between proteins at a disease state. This interaction occurs between a caspase and a protein that shows sequence homology to proteins involved in apoptosis (see for example page 22, lines 8-11), although there is no concrete indication that either this protein or its interaction with the caspase has any bearing on a disease condition or apoptosis; the biological relevance/importance of this prospective interaction is based solely on a predicted function of the unknown protein. However, the prediction of function based on sequence homology is an unpredictable art. This was demonstrated by the conflicting publications of Scott *et al.* (*Nature Genetics* **21**: 440-443, 1999; see entire document; henceforth Scott) and Everett *et al.* (*Nature Genetics* **17**: 411-422, 1997; see entire document; henceforth Everett) regarding the cloning and characterization of PDS. Everett initially identified and sequenced PDS, predicting based upon the sequence that the PDS gene product functioned as a sulphate ion transporter protein because of its similarity to a family of known sulphate ion transporters (see for example the Abstract and page 419, right column, second full

paragraph). However, further characterization done by Scott indicated that PDS was not a sulphate ion transporter because it was unable to transport sulphate ions; rather, Scott identified that PDS was a chloride and iodide ion transporter (see for example the Abstract and page 440, the paragraph bridging the left and right columns to the second full paragraph). Scott further indicated that their results underscored the importance of establishing function even in the face of significant homology to proteins of known function (see for example page 441, left column, third full paragraph), thereby establishing that function based on homology is an unpredictable endeavor. In light of the State of the Art, the skilled artisan would recognize the unpredictable nature of the instant invention.

Unpredictability of the art and Amount of experimentation required. When considering the nature of the invention, the broad scope of the invention, the guidance provided by the instant specification and the state/level of skill in the art, the skilled artisan would come to the conclusion that the claimed method is unpredictable in nature, and therefore the claimed invention is not enabled.

The invention encompasses embodiments where any disease state can be mapped in terms of protein-protein interactions simply by changing the redox state of the environment in which the interactions are tested; this is despite clear evidence that a multitude of diseases (such as numerous forms of cancer) result from genetic alterations that are irrespective of a redox state in the cellular environment. Thus, the skilled artisan could not predict what diseases could be mapped by the claimed method.

The instant specification makes use of a technique that has many pitfalls as it regards the purpose of the claimed method. The yeast two-hybrid system yields many false positives and

misses many interactions, and a number of these interactions that are missed may require the presence of a third protein (as indicated by Ito). Significantly, because the instant method is concerned with the interaction of mammalian genes, and these interactions are detected in a yeast cell, such a third protein would not be endogenous, resulting in even more missed interactions. Thus, when consulting the guidance provided by the instant specification and the State of the Art at the time of the invention, the skilled artisan would determine that the method would not predictably produce a complete map of the protein-protein interactions involved in any given disease; the incompleteness of the map then reflects upon an unpredictability regarding its use (i.e., is it being used properly if there are pieces that are missing).

Finally, as it regards the one potentially relevant interaction that is established in the instant specification, there is also a significant level of unpredictability. The reaction occurs between a protein involved in apoptosis (caspase) and a protein of unknown function, but with homology to protein involved in apoptosis. The specification mentions that this interaction reveals a new and specific approach to inhibiting apoptosis (see for example page 22, lines 8-13). However, neither the instant specification nor the prior art clearly establishes that this interaction is biologically relevant to apoptosis, nor do they establish that this unknown protein has any function during apoptosis. In fact, the prediction of function based on homology alone is unpredictable, as established by the comparison of the Everett and Scott references. Considering this fact in combination with the pitfalls of the two-hybrid system as a whole, the skilled artisan would not be able to predict which interactions were biologically relevant to a pathophysiological state. As a result, the skilled artisan could not predictably "causally

associate" such a protein interaction map with a disease state. Therefore the claimed method does not have an enabled real world use.

In conclusion, the claimed method would require undue and unpredictable trial and error experimentation on the part of the skilled artisan to make and use the claimed invention. There is no demonstration of the successful execution of the claimed method, where the only minimally described interaction with an apparent biological relevance contains a great deal of unpredictability. The method itself has many pitfalls as indicated in the prior art, where the instant specification does not remedy these deficiencies. Furthermore, the skilled artisan could not reasonably ascertain which diseases such a method could be used for. Each of these aspects would have to be determined or confirmed by empirical experimentation on the part of the skilled artisan. As a result, the indicated claims are found to lack enablement as required under 35 USC § 112, first paragraph.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 lacks a positive process step recapitulating the preamble of the claim. Specifically, the claim is directed to a method of identifying target proteins related to a disease, but does not contain a method step wherein these proteins are identified. Without such a step,

the claim is indefinite because there is no clear ultimate step to the claim, where the purpose of the method is achieved.

Claim 3 is indefinite because it is unclear what the method steps entail, or what they are directed to. It is unclear if the agents are directed to producing something (i.e., a modified protein), or if the agents are used to identify modified proteins (as in a derivatization assay, where only modified proteins react with the agent). It is unclear if the method is directed to the identification of modifications on a protein (i.e., what residues of the protein are modified), the identification of the proteins that are modified (i.e., what are the identities of the proteins that are modified), or if the identification of proteins that are subsequently modified by the modified proteins. It is further unclear if the agents are characteristic of the disease, if the protein modifications caused by the agents are characterized by the disease, or if the subsequently modified proteins that are modified by the agent-modified proteins are characterized by the disease. It is recommended that the steps of the method be clearly set forth (e.g., what steps are performed to identify the "target proteins", as well as what protein are the "target proteins" in the method) in order to allow the accurate examination of the claim.

Claim 5 lacks a positive process step recapitulating the preamble of the claim. Specifically, the claim is directed to a method of correlating protein interaction with oxygen tension, but does not contain a method step wherein a correlation is established. Without such a step, the claim is indefinite because there is no clear ultimate step to the claim, where the purpose of the method is achieved.

Claim 9 indicates that the method is directed to identify normal protein functions. However, it is unclear how normal protein functions can be determined in a situation where the

oxygen tension is different from that of room air. In other words, it is unclear how normal protein interactions can be determined when the conditions are changed from normal (i.e., yeast are normally grown at room air conditions, therefore normal protein functions would occur at room air conditions, and not at non-room air conditions).

Allowable Subject Matter

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Lambertson whose telephone number is (703) 308-8365. The examiner can normally be reached on 6:30am to 4pm, Mon.-Fri., first Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on (703) 305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

David A. Lambertson, Ph.D.
AU1636

JAMES KETTER
PRIMARY EXAMINER